REMARKS

Claims 65-84 are pending in the application. No amendments to the claims have been made by the present response.

Election/Restriction

From the comments at page 2 of the Office Action, applicants understand that claim 65 was found to be a linking claim and will be examined on the merits in accordance with PTO linking claim practice. Furthermore, applicants understand that if claim 65 is found allowable, the restriction of its comprised species will be withdrawn.

Information Disclosure Statement

At page 3 of the Office Action, the Examiner stated that the Information Disclosure Statement filed on October 6, 2003 has not been fully considered because a large number of references have been lost from the Office files. Applicants have herein enclosed replacement copies of the non-patent references requested by the Examiner.

35 U.S.C. § 112, Second Paragraph (Indefiniteness)

At page 4 of the Office Action, claims 65-71, 73, and 75-84 were rejected as allegedly indefinite. According to the Office Action, "it is not clear from the claims or the application what responses the Applicant considered to fall within the scope of Th1-like responses."

Applicants respectfully traverse the rejection in view of following remarks.

The meaning of the term "Th1" response is well known to one of ordinary skill in the art, and a brief description of a "Th1 response" is clearly set forth in the Background section of the specification (see page 1, lines 20-31). Th1 responses occur in an *in vivo* context (i.e., in the context of a whole organism). Claim 65 is drawn to a method of determining whether a fusion protein stimulates a response ("Th1-like") *in vitro* (i.e., in culture, outside of an organism). Although exhibiting many of the characteristic features of an *in vivo* Th1 response, the response of the claimed methods occurs *in vitro*, and is therefore differentiated as "Th1-like." Furthermore, the specification also clearly discloses multiple ways in which a "Th1-like" response can be detected, for example, by detecting the production of cytokines such as interferon (IFN)-gamma or tumor necrosis factor (TNF)-beta (see, e.g., page 1, lines 20-23; page 3, lines 7-8; page 21, lines 26-29; and page 22, lines 7-8).

In view of these considerations, applicants respectfully submit that independent claim 65 and the claims that depend therefrom satisfy the definiteness requirement. Applicants request that the Examiner withdraw rejection.

35 U.S.C. §103(a) (Obviousness)

At pages 5-8, of the Office Action, claims 65-69 and 76-84 were rejected as allegedly unpatentable over Lehmann et al. (U.S. Patent No. 5,939,281; herein referred to as "Lehmann") in view of Young et al. (U.S. Patent No. 6,335,183; herein referred to as "Young"). According to the Office Action,

> Lehmann teaches a method for determining the type of a T cell response induced by an antigen, in particular through the detection of a cytokine in a test sample....[T]he reference does not teach the application of such a method to fusion proteins as described by the present claims.
>
> ....
>
> Young teaches the enhancement of immune responses against an antigen by fusing the antigen to a heat shock protein, including the hsp65 of M. bovis....Thus it would have been obvious to those of ordinary skill in the art to use the method of Lehmann to determine the type and strength of the immune response induced by the fusion proteins of Young.

Applicants respectfully traverse the rejection in view of the following remarks.

The present invention is based, at least in part, on the inventors' discovery that a cell sample containing naïve lymphocytes can be stimulated with a fusion protein *in vitro* to exhibit a Th1-like response. Accordingly, independent claim 65 is drawn to a method of determining whether a fusion protein has the ability to stimulate a Th1-like response *in vitro*. The claimed methods require steps of (i) contacting, *in vitro*, a fusion protein and a cell sample containing naïve lymphocytes, and (ii) determining whether the fusion protein stimulates a Th1-like response in the cell sample. The specification clearly defines naïve lymphocytes as "lymphocytes that have not been exposed to the fusion protein (*in vivo* or *in vitro*) prior to their use in a method the invention" (see specification at page 2, lines 12-13).

Lehmann describes methods for detecting secreted cellular products, in particular secreted T-cell products, including cytokines. However, nowhere does Lehmann disclose or suggest the stimulation of a Th1-like response in naïve lymphocytes *in vitro* by contacting naïve lymphocytes with an isolated protein antigen, such as a fusion protein. A passage of Lehman (at column 2, lines 14-26) cited by the Examiner provides the backdrop for Lehmann's methods, stating that "[a]n ideal assay should permit monitoring all of the critical features of the T cell response: first, the existence of a response, i.e., that effector cells have been generated, second the nature of the effector cells as Th1 or Th2 type cells, and finally the magnitude of the response" (emphasis added). The cited passage makes clear that Lehmann's assays are intended to detect the presence and type of T cells that have been generated in a subject as a result of prior contact with an antigen (e.g., as a result of a viral antigen infection).

Consistent with the foregoing, Example 2 of Lehmann (at column 16) describes the isolation of primary lymphocytes from subjects that had been previously immunized with tetanus toxoid (TT). These cultured, TT-antigen-specific cells are then re-exposed to the TT antigen *in vitro* and analyzed for cytokine production. Lehmann also states in Example 5 (at column 22, lines 6-7) that the "secreting cells" identified by the screening method are "antigen-specific memory cells" (i.e., lymphocytes that have been previously exposed to the activating antigen). The cells that are detected *in vitro* in Examples 2 and 5 of Lehmann are thus clearly not "naïve lymphocytes," since they were taken from subjects that were previously exposed to the activating antigen.

Young does not add what is lacking in Lehmann. Young describes compositions of stress proteins or fusions of stress proteins with microbial antigens that are useful in generating an immune response in a subject (i.e., *in vivo*). Young does not disclose or suggest methods of stimulating a Th1-like response in naïve lymphocytes *in vitro* with a fusion protein. Because

Young does not cure the above-described deficiency in the disclosure of Lehmann, it does not, in combination with Lehmann, render obvious claims 65-69 and 76-84.

At page 7 of the Office Action, Suzue et al. (1997 Proc. Natl. Acad. Sci. USA 94:13146-15; herein referred to as "Suzue") and Anthony et al. (1999 Vaccine 17:373-83; herein referred to as "Anthony") were cited as further indication that production of IFN-γ by T-cells stimulated by hsp/antigen fusion proteins is associated with the induction of CTL responses. However, like Young, both Suzue and Anthony describe methods of generating an immune response *in vivo*, but do not disclose or suggest methods of contacting naïve lymphocytes with a fusion protein *in vitro*. The methods of Suzue generally involve administering (to a mouse) a fusion protein comprising an antigen (e.g., ovalbumin) and a bacterial heat shock protein (hsp) and subsequently testing CTL activity from isolated splenocytes (see, for example, Abstract; Figures 1-4; page 13148 column 1, line 22 to page 13149, column 2, line 11). Similarly, Anthony discloses methods of immunizing mice with a fusion protein comprising an antigen (e.g., HIV-1 p24) and a heat shock protein. Neither Suzue nor Anthony discloses or suggests methods of stimulating a Th1-like response in naïve lymphocytes *in vitro* with a fusion protein. As a result, these references do not cure the deficiencies of Lehmann and Young.

In view of these considerations, applicants respectfully request that the Examiner withdraw rejection.

At pages 8-10 of the Office Action, claims 65-71, 73, and 75-84 were rejected as allegedly unpatentable over Mizzen et al. (WO 98/23735; herein referred to as "Mizzen"), in view of Lehmann.

Applicants respectfully traverse the rejection in view of the following remarks.

As detailed above, independent claim 65 is drawn to a method of determining whether a fusion protein has the ability to stimulate a Th1-like response *in vitro*.

Mizzen discloses fusion proteins comprising a heat shock protein and an antigen and uses of such fusion proteins in stimulating an immune response in a subject (see, e.g., page 38, line 16 through page 39, line 24). However, nowhere does Mizzen disclose or suggest methods of stimulating a Th1-like response in naïve lymphocytes *in vitro* by contacting naïve lymphocytes with a fusion protein. As stated at page 9 of the Office Action, "the reference does not teach a method for the determination of whether a fusion protein induces a Th1-like response through stimulation of naïve lymphocytes in vitro, or methods involving the detection of IFN-γ production." As detailed herein in response to the previous obviousness rejection, Lehmann similarly lacks disclosure of methods of stimulating a Th1-like response in naïve lymphocytes *in vitro* by contacting the cells with an isolated protein antigen, such as a fusion protein. As a result, the combination of Mizzen and Lehmann do not render obvious the method of independent claim 65 or the claims that depend therefrom.

In view of these considerations, applicants respectfully request that the Examiner withdraw rejection.

Obviousness-Type Double Patenting

At pages 10-12 of the Office Action, claims 65-71, 73, and 76-84 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 6, 7, and 9-16 of commonly assigned U.S. Patent No. 6,495,347.

Included with this response is a disclaimer of the terminal portion of the term of the patent granted upon the present application subsequent to the expiration date of U.S. Patent No. 6,495,347. This terminal disclaimer overcomes the obviousness-type double patenting rejection.

CONCLUSION

Applicants submit that all grounds for rejection have been overcome and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 12071-002003.

Respectfully submitted,

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